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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,952	01/25/2001	Gregory Donoho	LEX-0118-USA	5907

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,952	DONOHO ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-4 is/are pending in the application.

4a) Of the above claim(s) 4 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-4 are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

[1] Claims 1-4 are pending in the application.

Election/Restrictions

[2] Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claim(s) 1-3, drawn to an isolated nucleic acid, classified in class 536, subclass 23.2.

II. Claim(s) 4, drawn to an isolated oligopeptide, classified in class 530, subclass 350.

[3] The inventions are distinct, each from the other because:

[4] The nucleic acid of Group I and the oligopeptide of Group II each comprises a chemically unrelated structure capable of separate manufacture, use, and effect. The nucleic acid of Group I has other utility besides encoding polypeptides such as being used as a hybridization probe and the oligopeptide of Group II can be made by another method such as purification from the natural source or chemical synthesis.

[5] MPEP § 803 sets forth two criteria for restricting between patentably distinct inventions – 1) the inventions must be independent or distinct and 2) there must be a serious burden on the examiner. MPEP § 803 states, "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02". Because the inventions of Groups I and II are distinct for the reasons given above, have separate classification, and each of the inventions requires a separate patent and non-patent literature and sequence search, restriction for examination purposes is proper.

[6] During a telephone conversation with David Hibler on April 10, 2003, a provisional election was made without traverse to prosecute the invention of Group I, claims 1-3.

[7] Applicant is reminded that affirmation of this election must be made in the response to this Office action even though the requirement be traversed (37 CFR 1.143).

[8] Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

[9] Claim 4 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Specification/Informalities

[10] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Nucleic Acid Encoding A Human Nitrilase Polypeptide". See MPEP § 606.01.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[11] Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Claim 1 is drawn to an isolated nucleic acid comprising at least 24 contiguous nucleotides of SEQ ID NO:1. Claim 2 is drawn to an isolated nucleic acid comprising a sequence that encodes SEQ ID NO:2 and hybridizes to SEQ ID NO:1 or a complement thereof under stringent conditions. Claim 3 is drawn to an isolated nucleic acid encoding SEQ ID NO:2. Applicant asserts the polypeptide of SEQ ID NO:2 encoded by the nucleic acid of SEQ ID NO:1 shares structural similarity with nitrilase proteins (page 2, lines 1-3 of the instant specification). A sequence search of SEQ ID NO:2 revealed an amino acid sequence disclosed by Pace et al. (*Curr Biol*

10:907-917, see particularly page 909, Figure 1) that is 100% identical to the amino acid sequence of SEQ ID NO:2 (see attached sequence comparison). The protein of Pace et al. (*Curr Biol* 10:907-917), identified as human Nit2, is disclosed as being a Nit nitrilase belonging to the Nit family of nitrilases (page 907, abstract and page 909, Figure 1). Pace et al. (*Genome Biol* 2:reviews0001.1-0001.9) disclose that the substrate and cell biology of the Nit family of nitrilases, including the enzymatic reaction, remain to be determined (page 000.4, Table I and page 0001.7, right column). Thus, while the polypeptide of SEQ ID NO:2 may belong to the nitrilase family of enzymes, one of ordinary skill in the art would recognize that further experimentation would be required to determine the substrate and reaction catalyzed by the polypeptide of SEQ ID NO:2, encoded by the nucleic acid of SEQ ID NO:1. Therefore, based on the evidence provided by Pace et al. (*Curr Biol* 10:907-917) and Pace et al. (*Genome Biol* 2:reviews0001.1-0001.9), an ordinarily skilled artisan would recognize that further research would be required to identify or reasonably confirm a "real world" context of use of the claimed invention. This type of utility is not considered a "substantial utility". See e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. Here the claimed polynucleotides are suitable only for additional research.

Applicant asserts various utilities for the claimed nucleic acids including protein expression, use as hybridization probes, antisense oligonucleotides, detection of mutations or polymorphisms for disease diagnosis, and as a therapeutic. Regarding the utilities of protein expression and use as hybridization probes or antisense oligonucleotides, virtually *any* nucleic acid has utility for protein expression and use as a hybridization probe or an antisense oligonucleotide. Regarding the use of the claimed nucleic acid for the detection of mutation or polymorphism for disease diagnosis or for use as a therapeutic, it is noted that the specification fails to disclose a mutation or polymorphism of the claimed nucleic acid that is related to a *specific* disease state that may be useful for identifying or diagnosing such disease state. Also, the specification fails to disclose a disease or condition that may be therapeutically treated using the claimed nucleic acid. Therefore, the asserted utilities are not specific to the claimed nucleic acids and are

instead general utilities that would be applicable to the broad class of nucleic acids. Thus, the claimed nucleic acids have no specific asserted utility. For the reasons stated above, the claimed nucleic acids have no specific and substantial utility or a well-established utility.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[12] Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is indefinite in the recitation of "first disclosed" (italics added for emphasis). As written, the claim has at least two interpretations: the claim can be interpreted as a nucleic acid comprising any subsequence of at least 24 contiguous nucleotides and the term "first disclosed" indicates novelty of the sequence of SEQ ID NO:1 OR the claim can be interpreted as meaning a nucleic acid comprising the first 24 contiguous nucleotides of SEQ ID NO:1, i.e., nucleotides 1-24 of SEQ ID NO:1. In the interest of advancing prosecution, the examiner has interpreted the claim as meaning a nucleic acid molecule comprising any subsequence of 24 contiguous nucleotides of SEQ ID NO:1 without regard to the assertion of novelty of SEQ ID NO:1. It is suggested that applicant clarify the meaning of the claim by replacing the term "nucleotide sequence first disclosed in SEQ ID NO:1" with, for example, "nucleotide sequence disclosed in SEQ ID NO:1".

b. Claim 2 is drawn to an isolated nucleic acid comprising a nucleotide sequence that encodes SEQ ID NO:2 **and** hybridizes under stringent conditions to SEQ ID NO:1 or the complement thereof. Claim 2 is indefinite in the recitation of "stringent conditions" as the specification fails to define those conditions which applicant intends as being stringent. It is noted that the specification defines hybridization conditions that are "highly stringent" (page 4, lines 10-13), "moderately stringent" (page 5, lines 20 and 21) and "low stringency" (page 10, lines 10-

13). However, there is no definition of the term "stringent conditions" and those hybridization conditions that are considered "stringent" varies widely in the art depending on the individual situation as well as the artisan making the determination. As such it is unclear how homologous to the sequence of SEQ ID NO:1 a nucleic acid molecule must be to be included within the scope of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[13] Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a genus of isolated nucleic acid molecules comprising at least 24 contiguous nucleotides of SEQ ID NO:1. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. The specification discloses only a single representative species of the claimed genus, i.e., SEQ ID NO:1. The specification fails to disclosure any other representative species of the claimed genus. As the claimed genus of nucleic acids has the potentiality of encoding many different proteins, including non-functional polypeptides or even polypeptides with function other than the asserted nitrilase activity, the genus of

claimed nucleic acids encompasses widely variant species. As such, neither the description of the structure and function of SEQ ID NO:1 nor the disclosure of a structural feature present in all members of the genus, i.e., at least 24 contiguous nucleotides of SEQ ID NO:1, is sufficient to be representative of the attributes and features of the entire genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

[14] Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in item above, one skilled in the art clearly would not know how to use the claimed invention.

[15] Even if applicants demonstrate the nucleic acids of claims 1-3 have a specific and substantial or well-established utility, the following rejection still applies. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the isolated nucleic acid of SEQ ID NO:1, does not reasonably provide enablement for all isolated nucleic acid molecules comprising at least 24 nucleotides of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Undue experimentation would be required for a skilled artisan to make and/or use the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The Factors most relevant to the instant rejection are addressed below.

- The claim is overly broad in scope: Claim 1 is so broad as encompass *all* isolated nucleic acid molecules comprising at least 24 nucleotides of SEQ ID NO:1, encoding polypeptides having *any* function,

including variants and fragments of SEQ ID NO:1. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleic acids broadly encompassed by the claims. In this case, the disclosure is limited to the isolated nucleic acid of SEQ ID NO:1.

- The lack of guidance and working examples: The specification provides a single working example of a nucleic acid comprising 24 contiguous nucleotides of SEQ ID NO:1, i.e., SEQ ID NO:1 encoding SEQ ID NO:2. This single working example fails to provide the necessary guidance for making and/or using the entire scope of claimed nucleic acids, which encompasses variants and fragments of SEQ ID NO:1 having *any* function. The specification fails to provide guidance regarding those regions or fragments of at least 24 contiguous nucleotides of SEQ ID NO:1 that are necessary for nitrilase activity and which of those fragments may be elongated with additional nucleotides and maintain nitrilase activity. Also, the specification fails to provide guidance as to methods of using those nucleic acids that do encode polypeptides having activity other than nitrilase activity, i.e., nucleic acids encoding non-functional polypeptides or those polypeptides having function other than nitrilase activity, which are encompassed by claim 1.

- The high degree of unpredictability of the art: The nucleotide sequence of an encoding nucleic acid determines an encoded protein's structural and functional properties. Predictability of which potential changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within an encoding nucleic acid's sequence where nucleotide modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide with the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been

provided in the specification. Thus, a skilled artisan would recognize the high degree of unpredictability that all nucleic acids comprising a fragment of as few as 24 nucleotides of an 831 nucleotide coding sequence, including fragments and variants of SEQ ID NO:1, would retain the ability to encode a protein having the asserted nitrilase activity.

- The state of the prior art: The state of the art provides evidence for the high degree of unpredictability as stated above. For example, Seffernick et al. (*J Bacteriol* 183:2405-2410) discloses two polypeptides having 98% amino acid sequence identity and 99% sequence identity at the nucleic acid level, differing at only 9 out of 475 amino acids (page 2407, right column, middle and page 2408, Figure 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page 2408, Figure 3), however, these polypeptides exhibit *distinct* functions. Thus, even though a first nucleic acid may share identical regions with a second nucleic acid, it is highly unpredictable as to whether the two nucleic acids encode proteins having identical functions.
- The amount of experimentation required is undue: While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the state of the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of claimed nucleic acids.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[16] It is noted that applicant claims benefit under 35 USC § 119(e) to provisional application serial number 60/179,000, filed January 28, 2000. The sequences of SEQ ID NO:1 and SEQ ID NO:2 are disclosed in the earlier filed provisional application. Applicant is thereby granted the benefit of the earlier filing date and the rejection stated below has been made based on a priority date of January 28, 2000.

[17] Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Database GenBank Accession Number G21250. Claim 1 is drawn to an isolated nucleic acid molecule comprising at least 24 contiguous bases of SEQ ID NO:1. Database GenBank Accession Number G21250 teaches an isolated nucleic acid comprising a fragment that is 100% identical to nucleotides 694-831 of SEQ ID NO:1 (see attached sequence comparison). This anticipates claim 1 as written.

Conclusion

[18] Claims 1-4 are pending.

[19] Claim 4 is withdrawn from consideration.

[20] Claims 1-3 are rejected.

[21] No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for Group 1600 is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

05/14/03